Neurodegeneration in multiple sclerosis is a process separate from inflammation: No

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We consider that there are at least two phases in multiple sclerosis (MS): relapsing–remitting MS (RRMS) and secondary progressive MS (SPMS) (let us leave aside from the moment the question of primary progressive MS). The two clinical phenotypes suggest different pathological processes, as has been confirmed by numerous neuropathological and magnetic resonance imaging (MRI) studies.

My argument is that SPMS, characterised by steadily progressive, predictive disability, cerebral and spinal cord atrophy and neuroaxonal death is, *purely and completely*, a secondary effect of the preceding and ongoing inflammatory disease process.

The disappearance of hand surgeons in rheumatology

The management of rheumatoid arthritis, the corresponding disorder in rheumatology, has been revolutionised in the last ten years by the active management of the inflammatory process. Thus secondary contracts, joint ankylosis and the need for prosthetic joint surgery has diminished by early medical intervention and the concept of ‘treating to target’ in rheumatology. Rheumatologists have the advantage over neurologists in that their target is easily seen and palpable. It is also measurable with accessible biomarkers and radiological changes. Neurologists do not have these luxuries; their target is hidden, as discussed below.


More inflammation causes worse neurodegeneration

Epidemiological and clinical evidence to support the primacy of inflammation as a predictor of secondary neurodegeneration in MS is extensive. We know that the frequency of relapse activity in the first two-five years after onset is predictive of the time of onset of secondary progressive MS, time to disability milestones such as Expanded Disability Status Scale (EDSS) 6.0, 8.0 and even time to death. These observations come from multiple database studies in France, Canada, Sweden and the UK. Treatment early in the course of RRMS using an only modestly effective anti-inflammatory therapy reduced the risk of death 21 years later by 47%.

The powerful evidence from international collaborations in genetics

Evidence from all the collaborative genetic studies indicate that the genes involved in the inflammatory process are of paramount importance in the pathogenesis of MS. Gene-ontology analyses based on the established MS risk loci have confirmed the role of these loci in T-cell mediated immunity; a primary neurodegenerative role appears to be negligible, but see recent work.

Grey matter atrophy is due to inflammation

Unseen grey matter inflammation is responsible for much of the disability accumulation in MS. This inflammation is hidden to the routine 1.5 T MRI scan and can only be detected by magnets with 7T strength or by special, research based, techniques. Thus the extensive subpial demyelination, atrophy of the thalamus and the basal ganglia cannot be assessed by our routine MRI techniques. Although the inflammatory component in the grey matter appears less than that seen in white matter, there is no doubt that, for example, the cortical ribbon demyelination and overlying meningeal inflammation is highly correlated and is most intense near granulomatous meningeal inflammatory change.

Presently used measures miss most of the neuroinflammation

We also know that, even with clinical and MRI monitoring on a regular basis, as recommended by the 2013 revisions, we miss a significant proportion of the inflammatory burden of MS disease activity. MRI scanning, as used in routine clinical practice, does not detect grey matter disease in the cortex and sub-cortical structures such as the thalamus and the basal ganglia. It also does not detect the diffuse white matter inflammatory pathology in apparently unaffected deep white matter. We know that even in patients presenting with their first demyelinating event, the clinically isolated syndrome (CIS), that there is significant cortical atrophy. Cortical atrophy progresses, without treatment, at a rate of loss of 0.4% brain volume change in patients in the first few years of their disease. My argument is that this is due to undetected inflammatory grey matter disease. In a previous ‘Controversy’ we had discussed the urgent need for much more sensitive biomarkers to detect this hidden inflammatory burden. The evidence is that only by regular monitoring of cerebrospinal fluid neurofilaments can we hope to assess this occult grey matter disease activity.

The overwhelming need for biomarkers in relapsing MS

A natural logical extension of this hypothesis of the primacy of inflammation is that, if we can abolish inflammation early in the disease course (in the first few years), we can prevent the onset of SPMS. The term ‘the window of opportunity’ was introduced by Alasdair Coles many years ago. The accumulating evidence from studies of patients with CIS is that even at that stage there are significant deficits in cognition and grey matter pathology. Very conservative guidelines exist in the UK requiring two or more clinically significant relapses in the previous two years before therapy is introduced. Conservative neurologists in the UK, Ireland, Australia and New Zealand tend not to initiate disease modifying therapy (DMT) in patients with CIS with; the rest of the world introduces a DMT at this stage. I suspect in the future that, if six months after a CIS episode, there was evidence of ongoing white matter inflammation (by MRI scanning) or white/grey matter tissue destruction (by cerebrospinal fluid neurofilaments), DMTs will be immediately started.

Inadequate detection of inflammation = inadequate use of therapies

Why we have not succeeded in abolishing SPMS is essentially because we do not have the tools to measure the inflammatory burden in the important first few years of the disease process. We have excellent drugs, which cover a range of the spectrum of the disease activity in MS. We do not know how to use them properly and therefore do not use them properly. Patients often sustain significant loss of tissue due to inflammation in the early years because we cannot detect it and because we are slow to escalate therapy.
Better inflammatory biomarkers are needed: MRI has inadequate sensitivity
If there was sensitive measurement of ongoing inflammation in routine use, which we could apply, at 3 monthly or 6 monthly intervals, to gauge the effectiveness of any therapy we could devise an algorithm to guide clinicians in much more rapid escalation of disease modifying therapy. Such patients with more active disease might thus be identified early and moved from first-line to therapies for highly active disease over the first year or two of their illness. Similarly patients who appear to be controlled well by clinical and MRI criteria, but who have ongoing grey matter disease, could be identified. To this observer it would seem that the only biomarker that has this potential is the examination of the cerebrospinal neurofilaments.

The need for neuroprotection does not imply primary neurodegeneration
While atrophy is a feature of MS pathology at all stages of the disease process and can be seen in patients at their initial presenting demyelinating event, I do not accept that this indicates two separate independent processes, inflammation and neurodegeneration. I do accept that we have to protect neurons and axons from the effects of demyelination thus we need neuroprotective therapies; encouraging results from the study of simvastatin in progressive MS and the work of the Progressive Multiple Sclerosis Alliance indicate the importance of neuroprotection.

The principle of parsimony
As well as of the above arguments, I have one essential philosophical argument, the principle of parsimony, Occam’s razor. If a reasonable explanation for the observed clinical and pathological features in MS can be attributed to a single process, why invoke two separate independent processes?

Conflict of interest
Michael Hutchinson served on a medical advisory board for the CONFIRM study [BG00012] for Biogen-Idec, serves on the editorial board of the Multiple Sclerosis journal, has received speaker’s honoraria from Novartis, Biogen Idec and Bayer-Schering and receives research support from Dystonia Ireland, the Health Research Board of Ireland and the European Dystonia Foundation.

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References


